Prevalence of serious adverse pregnancy outcomes after exposure to interferon beta before or during pregnancy: stratification by characteristics of pregnant women with MS in a register-based cohort study in Finland and Sweden

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INTRODUCTION

- Observational studies[1–5] and a large post-authorization safety study[6] in pregnant patients with multiple sclerosis (MS) have reported no increase in the prevalence of adverse pregnancy outcomes after exposure to any interferon beta (IFN β) before or during pregnancy.
- However, the prevalence of adverse pregnancy outcomes by maternal characteristics is unknown.

OBJECTIVE

- To describe the prevalence of serious adverse pregnancy outcomes (SAPOs) among pregnant patients with MS exposed to IFN β only and those unexposed to any MS disease-modifying drugs (DMDs), stratified by maternal characteristics.

METHODS

Study design and settings

- In this cohort study, healthcare registry data from Finland (1996–2014) and Sweden (2005–2014) were used to study pregnancy outcomes in patients with MS.

Study population

- Patients who were pregnant during the study period, with the pregnancy ending in elective termination (only in Finland), stillbirth, or live birth. The exposure groups were pregnancies among patients with MS:
  - dispensed only IFN β ≤6 months prior to date of last menstrual period (LMP) or during pregnancy (IFN β–exposed)
  - without any dispensed MS DMD (unexposed).

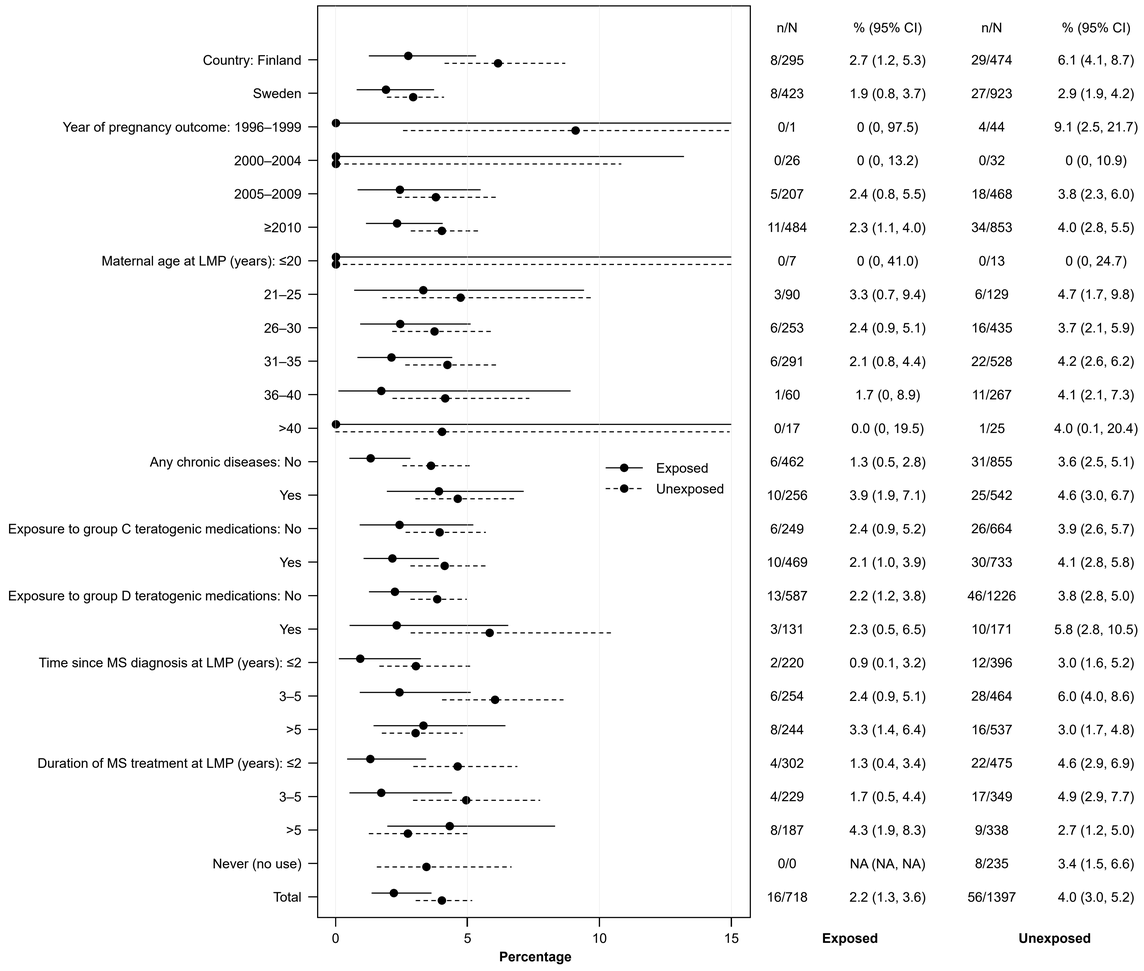
Outcome

- The composite outcome – SAPO – consisted of elective termination due to fetal anomaly, live birth with major congenital anomaly, or stillbirth.

Statistical analysis

- The prevalence (%) of SAPO, with 95% confidence interval (CI), was analyzed for IFN β–exposed and unexposed groups, with stratification by maternal characteristics at LMP.

Figure. Prevalence of SAPO stratified by maternal characteristics



	n/N	% (95% CI)	n/N	% (95% CI)
	Exposed		Unexposed	
Country: Finland	8/295	2.7 (1.2, 5.3)	29/474	6.1 (4.1, 8.7)
Sweden	8/423	1.9 (0.8, 3.7)	27/923	2.9 (1.9, 4.2)
Year of pregnancy outcome: 1996–1999	0/1	0 (0, 97.5)	4/44	9.1 (2.5, 21.7)
2000–2004	0/26	0 (0, 13.2)	0/32	0 (0, 10.9)
2005–2009	5/207	2.4 (0.8, 5.5)	18/468	3.8 (2.3, 6.0)
≥2010	11/484	2.3 (1.1, 4.0)	34/853	4.0 (2.8, 5.5)
Maternal age at LMP (years): ≤20	0/7	0 (0, 41.0)	0/13	0 (0, 24.7)
21–25	3/90	3.3 (0.7, 9.4)	6/129	4.7 (1.7, 9.8)
26–30	6/253	2.4 (0.9, 5.1)	16/435	3.7 (2.1, 5.9)
31–35	6/291	2.1 (0.8, 4.4)	22/528	4.2 (2.6, 6.2)
36–40	1/60	1.7 (0, 8.9)	11/267	4.1 (2.1, 7.3)
>40	0/17	0.0 (0, 19.5)	1/25	4.0 (0.1, 20.4)
Any chronic diseases: No	6/462	1.3 (0.5, 2.8)	31/855	3.6 (2.5, 5.1)
Yes	10/256	3.9 (1.9, 7.1)	25/542	4.6 (3.0, 6.7)
Exposure to group C teratogenic medications: No	6/249	2.4 (0.9, 5.2)	26/664	3.9 (2.6, 5.7)
Yes	10/469	2.1 (1.0, 3.9)	30/733	4.1 (2.8, 5.8)
Exposure to group D teratogenic medications: No	13/587	2.2 (1.2, 3.8)	46/1226	3.8 (2.8, 5.0)
Yes	3/131	2.3 (0.5, 6.5)	10/171	5.8 (2.8, 10.5)
Time since MS diagnosis at LMP (years): ≤2	2/220	0.9 (0.1, 3.2)	12/396	3.0 (1.6, 5.2)
3–5	6/254	2.4 (0.9, 5.1)	28/464	6.0 (4.0, 8.6)
>5	8/244	3.3 (1.4, 6.4)	16/537	3.0 (1.7, 4.8)
Duration of MS treatment at LMP (years): ≤2	4/302	1.3 (0.4, 3.4)	22/475	4.6 (2.9, 6.9)
3–5	4/229	1.7 (0.5, 4.4)	17/349	4.9 (2.9, 7.7)
>5	8/187	4.3 (1.9, 8.3)	9/338	2.7 (1.2, 5.0)
Never (no use)	0/0	NA (NA, NA)	8/235	3.4 (1.5, 6.6)
Total	16/718	2.2 (1.3, 3.6)	56/1397	4.0 (3.0, 5.2)

CI, confidence interval; LMP, last menstrual period; MS, multiple sclerosis; NA, not available; SAPO, serious adverse pregnancy outcome.

RESULTS (Figure)

- Among 718 IFN β–exposed and 1397 unexposed pregnancies stratified by maternal age, point prevalence of the SAPO appeared to decrease with increasing maternal age among IFN β–exposed pregnancies but not among unexposed pregnancies, across the strata. However, CIs for the prevalences were wide and overlapping.
- Among IFN β–exposed pregnant patients with chronic disease, prevalence of the SAPO appeared similar among the exposed and unexposed groups.
- Prevalence of the SAPO appeared comparable among the IFN β–exposed and unexposed groups when MS was diagnosed ≤2 years, 3–5 years, or >5 years before the LMP.
- When stratified by duration of MS treatment, prevalence of the SAPO was not increased in the IFN β–exposed versus unexposed group in the strata of ≤2-year treatment and 3- to 5-year treatment. Point prevalence of the SAPO appeared descriptively increased among the exposed group with >5-year treatment, versus the unexposed, but CIs were wide and overlapping, indicating no statistical difference.

METHODOLOGIC CONSIDERATIONS

- Stratified prevalences should be interpreted with caution, as the descriptive prevalences were not controlled for confounding.
- However, *post hoc* interaction analyses with confounder adjustment strengthened the result that maternal characteristics did not modify adverse event risk.

CONCLUSION

- In this population-based observational study, descriptive prevalence of the composite SAPO appeared similar with IFN β exposure before or during pregnancy, when pregnant patients with MS were stratified by maternal characteristics.

DISCLOSURES

MK, KMH, RK, and **PK** are employees of StatFinn–EPID Research, which performs commissioned pharmacoepidemiologic studies for several pharmaceutical companies**. SaB** was and **ShB** is an employee at the Centre for Pharmacoepidemiology, which receive grants from several entities including pharmaceutical companies. **YG** is an employee of Novartis Pharma AG. **MS** is an employee of Merck KGaA, Darmstadt, Germany. **AK** is an employee of Biogen. **KS-W** is an employee of Bayer AG. **JH** has received research funding from Bayer-Schering, Biogen, Merck Serono, Novartis, Sanofi Genzyme, Teva, Swedish Research Council, Swedish Brain Foundation; consulting fees from Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi-Genzyme, Teva; and speakers bureau honoraria from Bayer Schering, Biogen, Merck Serono, Novartis, Sanofi Genzyme, Teva. **AV-A** has received research funding from Sanofi; consulting fees from Biogen, Genzyme, Grifols, Merck, Novartis, Roche, Sanofi; and speakers bureau honoraria from Biogen, Genzyme, Grifols, Merck, Novartis, Roche, Sanofi. **SM** has received research funding from AstraZeneca, IQVIA, Novartis, Roche; and speakers bureau honoraria from Teva.

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